Avatars of adipose tissue: the saga of transformation of white fat, the villain into brown fat, the protector. Focus on “Inflammation induced by RAW macrophages suppresses the UCP1 mRNA induction via ERK activation in 10T1/2 adipocytes”

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THE WORD “AVATAR” (ævəˈtər) OR “AVATAAR” (əvəˈtɑːr) IS DERIVED FROM THE Sanskrit root word “avatāra,” which means “incarnation,” “manifestation,” “embodiment,” or “transformation,” or “transformation” of someone in a different shape or form. Adipose tissue is a depot of fat (triglycerides) that serves as the body’s energy reserves in addition to functioning as an endocrine organ that synthesizes and secretes important metabolic regulatory molecules including hormones and adipokines (9, 16). Adipose tissue in mammals is present mainly in two forms (avatars): 1) white adipose tissue (WAT) and 2) brown adipose tissue (BAT). Obesity caused by excess WAT is associated with insulin resistance, diabetes, cardiovascular risk, and other metabolic syndromes (8). Hence, WAT is considered as the bad avatar of the adipose tissue. On the other hand, BAT utilizes stored fat as the substrate to generate energy (heat) for protection against hypothermia (adaptive thermogenesis), through the uncoupling of oxidative phosphorylation by the uncoupling protein-1 (UCP-1), and thereby, compromising ATP production in mitochondria (12). In human adults, a significant abundance of adipocytes expressing UCP-1, especially in the supraclavicular and neck areas, has been observed (5, 17). These UCP-1-expressing adipocytes are considered to be “brown-like adipocytes” (BLAs), a feature of the BAT avatar. The BLAs emerging from the WAT boost the norepinephrine-induced oxygen consumption and improve insulin sensitivity and are more abundant in mice resistant to obesity (1, 3, 7, 11, 15). Moreover, the actions of BAT are associated with marked suppression of weight gain, control of body weight, a healthy phenotype, and regulation of glucose and fat metabolism. By contrast, a lack of BAT activity leads to obesity and metabolic disorders. Therefore, BAT is regarded as the good avatar of adipose tissue.

The BLAs emerge from the WAT upon certain physiological stimuli and pharmacological treatments (2, 4, 6, 10). It is crucial to identify precisely the physiological cues/factors that are responsible for the transformation (in this context equated with transdifferentiation) of WAT into BLAs in vivo. Currently, there are certain constraints in demonstrating and establishing the expression of UCP-1 as the marker of transdifferentiation of WAT into BLAs (the BAT avatar) in experimental animal models because of the complexity of factors that induce UCP-1 in vivo. To overcome those constraints encountered in the in vivo models, in this issue of American Journal of Physiology-Cell Physiology, Sakamoto et al. (13) have conducted an ingenious study by utilizing an in vitro coculture cellular model, consisting of RAW macrophages and C3H10T1/2 adipocytes, to identify the molecular and trans-cellular regulation of UCP-1 expression in adipocytes (WAT surrogate) as a marker of BLAs. The authors show that norepinephrine, acting via β-adrenergic receptors, CAMP, protein kinase A, and nuclear signaling, induces the expression of UCP-1 mRNA in adipocytes. Furthermore, the authors demonstrate that lipopolysaccharide (LPS)-challenged macrophage conditioned medium and tumor necrosis factor-α (TNF-α) suppress the induction of UCP-1 mRNA in adipocytes through extracellular signal-regulated kinase (ERK) activation and subsequent blockade of the nuclear signaling. The study by Sakamoto et al. (13) clearly reveals the β-adrenergic stimulation and macrophage- and TNF-α-promoted suppression of UCP-1 mRNA expression in white adipocytes, suggesting that the β-adrenergic pathway induces and the activated macrophages (by LPS) and TNF-α suppress the transformation of white adipocytes into BLAs (the BAT avatar), and implying that inflammation suppresses the emergence of BLAs from white adipocytes.

However, the study by Sakamoto et al. (13) has not (as the authors note) unequivocally demonstrated the induction of UCP-1 by epinephrine/norepinephrine in the macrophage cell line. In this study, the authors utilized RAW 264.7 macrophages, derived from the inflammation mediator-activated macrophage cell line, which express low levels of UCP-1. The authors note that epinephrine/norepinephrine may produce a greater UCP-1 response in response to the adipocytes derived from the C3H10T1/2 adipocytes, which express high levels of UCP-1. The authors also note that the macrophages used in the study were not derived from the inflammation mediator-activated macrophage cell line, which may have a different response to UCP-1 induction in response to epinephrine/norepinephrine. Therefore, further studies are needed to confirm the induction of UCP-1 by epinephrine/norepinephrine in the macrophage cell line, which may provide a greater understanding of the role of inflammation in the transformation of white adipocytes into BLAs.

Fig. 1. Schematic representation of mechanisms of adrenaline induction and suppression of transdifferentiation of brown-like adipocytes (BLAs) from the white adipocytes (WAT) through the action of β-adrenergic receptors (β-AR) and by TNF-α derived from the inflammation mediator-activated macrophages. Activation of macrophages either towards induction or suppression of transdifferentiation of BLAs is critical for the BAT activity. UCP-1, uncoupling protein-1.
UCP-1 protein. This could be due to 1) the detection limits of the expressed protein, 2) protein turnover (time-dependent degradation by proteolysis), and 3) loss of protein during assay. In situ localization by confocal immunofluorescence microscopy (14) on an appropriate timescale could offer insights into the UCP-1 protein expression in the white adipocytes. Moreover, one should bear in mind that the authors used the 10T1/2 adipocyte cell line, which may have limited the detection of UCP-1 protein, as several cell lines have problems in detecting certain proteins (unpublished observations). This limitation of the findings of Sakamoto et al. may be rectified by using isolated, sorted primary BLAs from animals. In this regard, a thorough investigation of WATs from different locations, including from abdominal, subcutaneous, and epididial fat, should be conducted to establish the abundance and isolation of homogenous BLAs. Such an approach may provide a thorough understanding of the regulation of transformation of white adipocytes into brown adipocytes. Also, it is critical to explore other putative signaling pathways involving other hormones (besides epinephrine) and protein kinases (in addition to ERK).

Overall, the study of Sakamoto et al. (13) is a breakthrough that advances understanding of the regulation of induction of BAT from WAT. Subsequent work should incorporate the authors’ approach in efforts that seek to enhance the actions of BLAs (by hormonal or pharmacological treatments or by suppressing or controlling inflammation) with elevated UCP-1 expression in obese animal models, towards correcting the obesity-mediated insulin resistance, hyperglycemia, and cardiovascular diseases. One important finding of this study is that macrophage activation can lead either to the induction or to the inhibition of BLA activity (Fig. 1). In this scenario, the type of activation of macrophages is critical: inflammatory activation (e.g., by LPS) suppresses the expression of UCP-1 and induction of the BLA activity in white adipocytes. However, this needs to be established in animal models in vivo. Of note, macrophages produce catecholamines (epinephrine and norepinephrine) under certain conditions; their production should be taken into consideration and the mechanisms that regulate production of epinephrine by macrophages and its BLA-inducing actions in the WAT need to be established in vivo (Fig. 1). We believe that it is not farfetched but hopeful to envision that invigorating the emergence of the BAT avatar (the protector) from the WAT avatar (the villain) can become the fulcrum to overcome and/or treat obesity-mediated/associated diseases in the near future.

REFERENCES


